IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

COLMAN *et al.*

Appl. No: 09/475,674

Filed: December 30, 1999

For: **Method of Preparing a Somatic Cell for Nuclear Transfer**

Art Unit: 1632

Examiner: Crouch, D.

Atty. Docket: 1966.0020001/EKS/BJD

Preliminary Amendment and Remarks

Commissioner for Patents
Washington, D.C. 20231

Via Hand Carry to Examiner D. Crouch
Art Unit 1632

Sir:

In advance of prosecution of the Continued Prosecution Application filed in the above-captioned matter on January 18, 2001, please amend the application as follows:

Amendments

In the Claims:

Please amend the claims as follows:

1. (Once amended) A method of preparing a somatic cell for nuclear transfer comprising modifying the [genetic material] nuclear genome of the somatic cell at an endogenous locus by a genetic targeting event.

3. (Twice amended) The method, as claimed in claim 1, wherein the modification is [inactivation of a gene,] removal of a gene, modification of a gene, upregulation of a gene, gene replacement or transgene placement.

Please add the following new claims:

-- 62. The method of claim 12, wherein said region of homology is greater than 7 kb in length.

63. The method of claim 1, wherein the modification is inactivation of a gene.

64. The method of claim 1, wherein said G_0 cell is obtained by serum starvation of a somatic cell. --

Remarks

I. Support for Amendments

The foregoing amendments to the claims are fully supported in the application as filed, and add no new matter. Specifically, support for the amendments to claim 1 may be found in the specification at page 4, lines 13-21; at page 6, line 25; at page 13, line 8; at page 33, line 14; at page 35, lines 1, 14 and 27; at pages 29-30; at page 37, lines 4, 7 and 9; at page 49, line 27; at page 51, lines 2-5; at page 56, lines 19-20; at page 66, line 22; and at page 69, line 3. Support

for new claim 62 may be found in the specification at page 7, lines 25-27; support for new claim 63 may be found at page 29, lines 13-15, and in claim 3 as originally filed; and support for new claim 64 may be found at page 51, lines 2-5. Accordingly, the foregoing amendments add no new matter, and their entry and consideration are respectfully requested.

II. Status of the Claims

By the foregoing amendments, claims 1 and 3 have been amended and new claims 62-64 are sought to be entered. These amendments do not add new matter to the application. Upon entry of the foregoing amendments, claims 1-17, and 62-64 are pending in the application, with claim 1 being the sole independent claim.

III. Summary of the Office Action

Applicants note that a non-final Office Action was issued in the present application on July 18, 2000 (Paper No. 6). In advance of prosecution of the Continued Prosecution Application, Applicants wish to provide the following remarks concerning certain elements of the Office Action.

In the Office Action, the Examiner made six rejections of the claims. Applicants offer the following remarks concerning each of these elements of the Office Action, in view of the foregoing amendments.

IV. The Double-Patenting Rejection

In the Office Action at pages 2-3, the Examiner provisionally rejected claims 1-3, 5, 9, 10, 12, 13, 16 and 17 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 24 and 25 of commonly owned, co-pending U.S. Appl. No. 09/377,595 (hereinafter "the '595 application"). Applicants respectfully traverse this rejection.

Initially, Applicants note that in making this rejection, the Examiner refers to Example 3 of the '595 application. However, this example does not involve genetic targeting, and therefore would appear not to be germane to the patentability of the presently claimed invention. Where genetic targeting is disclosed in the '595 application, the context of this disclosure must be appreciated. The use of homologous recombination in the '595 application is with regard to insertion into a site which either possesses a previously and randomly inserted (*i.e.*, untargeted) selectable marker OR a site containing a previously and randomly inserted (*i.e.*, untargeted) endonuclease recognition site. The homologous recombination methods disclosed in the '595 application *would not work without the prior insertion of the above facilitating sequences.*

Hence, in the '595 application, gene targeting can only be used at a site which has been empirically prepared. This is described in the specification of that application as the "ninth aspect" of the invention disclosed and claimed in the '595 application:

> A ninth aspect of the invention provides a process for targeting a transgene to a location of interest. The process may comprise: selecting a nuclear donor cell produced by the second aspect of the invention, specifically, wherein the transgene is flanked by a recognition site for a site specific recombinase and a recognition site for a rare cutting endonuclease; or selecting a reconstituted animal embryo which has been produced by the fourth aspect of the invention which includes a transgene which is flanked by the same loci; or an animal developed from such a reconstituted animal embryo, and using a gene targeting vector, preferably

> isogenic to the host cell, to place a target transgene at the target locus.

Specification of '595 application at page 25, lines 6-19. Elsewhere in the specification of the '595 application, it is stated that:

> A site which supports favourable expression is identified using a transgene construct linked to a counter-selectable marker, e.g. the Herpes simplex tk gene, loss of which can be selected by the drug ganciclovir or the HPRT (Hypoxanthine phosphoribosyl transferase) gene, loss of which can be selected by the drug 6-thioguanine in cells lacking endogenous HPRT activity, or the Aequoria Victoria green fluorescent protein gene (Chalfie, M. et al., 1994, Science 263, 802-805) loss of which can be detected visually. DNA regions flanking the integrated transgene are cloned and incorporated into a replacement gene targeting vector.

Specification of '595 application at page 29, lines 3-14. Thus, in order to accomplish gene targeting according to the methods disclosed in the '595 application, a target site must first be incorporated into the genomic locus which is to become the recipient of the transgene, prior to carrying out the recombination reaction that results in the incorporation of the transgene.

The present invention differs from that of the '595 application in that gene targeting carried out according to the presently claimed invention does not require the prior insertion of such a target site. In contrast, it facilitates efficient homologous recombination to target any predetermined or preselected genetic locus. Moreover, the finding that genetic targeting did not require such elaborate preparation steps was surprising, and it is self-evidently advantageous.

In summary, then, the earlier '595 application teaches that genetic targeting requires the insertion of an artificial locus, while the present application shows that, surprisingly, gene targeting can proceed at a wild-type or naturally occurring endogenous locus in a cell without the need for such prior modification. To highlight this distinction, claim 1 has been amended to

specify that such "recombination enhancing" features are not present, and that the genetic modification occurs at a naturally occurring (*i.e.*, endogenous) genetic locus. In so doing, Applicants respectfully assert that the invention as presently claimed is patentably distinct from, and is not obvious over, the invention disclosed and claimed in the '595 application. Hence, the obviousness-type double patenting rejection made in the previous Office Action should not be maintained.

V. The Enablement Rejection of Claims 1-13, 16 and 17

In the Office Action at pages 4-6, the Examiner rejected claims 1-13, 16 and 17 under 35 U.S.C. § 112, first paragraph, for lack of an enabling disclosure. Applicants respectfully traverse this rejection.

In making this rejection, the Examiner first contended that:

> [t]he specification only defines abundantly expressed loci as being the either the [sic] collagen gene locus or the β-lactoglobulin locus. There is no general definition of the term or means to determine other loci that are "abundantly expressed".

Office Action at page 4, forth paragraph, lines 1-3. Applicants respectfully disagree with these contentions. The specification (at page 7, lines 11*ff*) specifically describes the preferable use of a genetic target which is actively transcribed or is adjacent to a genetic locus which is actively transcribed. The specification also describes how other such other intermediately or "abundantly expressed loci" can be identified on the basis of mRNA expression as described in an undergraduate text book which is well-known to those of ordinary skill in the relevant art:

> Suitable genes would produce mRNAs which fall into the arbitrarily defined intermediate, or abundant class of mRNAs which are present at 300 or more copies of each molecule per cell

(Alberts et al. 1994, Molecular Biology of the Cell, Garland Publishing, New York and London).

Specification at page 7, lines 11-14. Hence, although genetic targeting of the collagen and β-lactoglobulin loci are specifically exemplified in the present application, the scope of the claimed invention is not limited to these loci since the present specification enables one of ordinary skill to identify other loci that are "abundantly expressed," as the meaning of that term is understood in the art. Moreover, methods for determining the level of expression of a particular locus (*i.e.*, whether or not the locus is "abundantly expressed" as that term is defined in the specification) are well-known in the art and are described throughout the Examples in the present specification (*e.g.*, Northern blotting as used in the Examples).

In order to enable a claimed invention, a specification need not teach, and preferably omits, information that is well-known to those of ordinary skill in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1463 (Fed. Cir. 1984); *In re Wands*, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988). Further, the scope of enablement of the specification need only "bear a reasonable correlation" to the scope of the invention as claimed. *See in re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970), *followed by Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). In addition, one of ordinary skill is deemed to know what is considered well-known in the art. *See In re Howarth*, 210 USPQ 689, 692 (C.C.P.A. 1981). Thus, based on the disclosure contained in the specification and information that is readily available in the art, Applicants respectfully assert that one of ordinary skill could readily determine, without resorting to undue experimentation, whether a given locus is "abundantly expressed." This portion of the rejection therefore should not be maintained.

At page 5, lines 1-2 of the Office Action, the Examiner also contended that the specification only teaches genetic targeting via homologous recombination, and does not teach any other means of targeting a particular genetic locus. Applicants respectfully disagree with these contentions, and respectfully assert that, based on the present specification in view of information that was known in the art, one of ordinary skill could readily carry out genetic targeting of a particular locus by methods other than homologous recombination. Therefore, Applicants respectfully assert that this portion of the rejection should not be maintained.

Finally, the Examiner contended at pages 5-6 of the Office Action that the art at the time of filing of the present application "recognized that the cloning of mammals required a process where the donor nuclei . . . were reprogrammed . . . . " and that the present specification only discloses serum starvation as a means for such reprogramming. Applicants respectfully disagree with these contentions. While serum starvation is the selected method used for making G_0 donor cells in the Examples in the present application (*see, e.g.*, specification at page 51, lines 2-5), it certainly is not the only means of inducing cells to enter the quiescent (*i.e.*, G_0) phase of the cell cycle. Other methods of accomplishing this reprogramming, such as chemical treatments, growth inhibition or manipulation of gene expression, were well-known in the art at the time of filing of the present application (*see, e.g.*, WO 97/07669; Doc. No. AM1, of record, which was incorporated by reference into the present application; *see* specification at page 1, lines 21-23). Moreover, the specification clearly states (*e.g.*, at page 8, line 29; and at page 9, line 9) that the method of nuclear transfer is not limited -- any method of nuclear transfer (and hence, any method of reprogramming) may be used in accordance with the methods of the presently claimed invention. Furthermore, other methods of preparing cells as nuclear donors for production of

transgenic animals, using cells from different stages of the cell cycle were known in the art at the time of filing of the present application (*see, e.g.*, WO 98/39416, WO 98/30683, WO 98/07841, WO 97/37009, WO 98/27214, WO 99/01163 and WO 99/01164; all of which are referred to in the present specification at page 1, lines 25-27).

As the Federal Circuit has held:

> [t]he purpose of [the enablement] provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and knowledge in the art.

Scripps Clinic & Research Foundation v. Genentech, Inc., 18 USPQ2d 1001, 1006 (Fed. Cir. 1991). As discussed above, the present specification and knowledge that is readily available in the art (and which the ordinarily skilled artisan is deemed to know) provide guidance concerning how to identify an abundantly expressed locus, how to carry out genetic targeting, and how to reprogram cells for preparation of the cells as nuclear donors. Therefore, Applicants respectfully assert that the specification as filed fully enables the scope of the invention as presently claimed. Hence, the rejection of claims 1-13, 16 and 17 under 35 U.S.C. § 112, first paragraph for lack of enablement, made in the previous Office Action, should not be maintained.

VI. The Enablement Rejection of Claims 14 and 15

In the Office Action at pages 6-7, the Examiner rejected claims 14 and 15 under 35 U.S.C. § 112, first paragraph, for lack of an enabling disclosure. Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contended that the specification does not provide adequate guidance as to the means for artificially inducing gene expression or for causing chromatin changes in order to stimulate transcription at a target locus. Citing *Genentech v. Novo Nordisk a/S*, 42 USPQ2d 1001 (Fed. Cir. 1997), the Examiner concluded that Applicants have "only throw[n] out a germ of an idea with regards to claims 14 and 15." Office Action at page 7, lines 13-22. Applicants respectfully disagree with these contentions.

The present specification provides ample disclosure of art-known methods of inducing gene expression and/or chromatin changes in a target locus, particularly at page 27, line 25, through page 29, line 3. For example, the cited literature (particularly Chen *et al*, cited in the specification at page 28, line 4) describes in detail how chemical reagents such as sodium butyrate or trichostatin A are used to reactivate silent genes. Similarly, the specification at page 28, lines 10-21, discusses, with detailed citations, gene activation using transcriptional activators.

Hence, the specification discloses the use of methods of inducing gene expression and/or chromatin changes that are well-known in the art, and provides precise literature citations in support thereof. The point of novelty of the claimed invention is not what methods are used to induce gene expression or to modify the chromatin of a given genetic locus, and these methods were well-known to those of ordinary skill in the art at the time that the present application was filed. Therefore, as noted above, under *Hybritech*, *Lindemann Maschinenfabrik*, *Wands*, and *Howarth* the present specification need not teach, and preferably omits, this particular information.

Further, the scope of enablement of the specification need only "bear a reasonable correlation" to the scope of the invention as claimed. *See in re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970), *followed by Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). In addition, one of ordinary skill in the art is deemed to know not only what is considered well-known, but also where to search for any needed starting materials. *See In re Howarth*, 210 USPQ 689, 692 (C.C.P.A. 1981). As discussed above, the sources and methods for using a variety of means of inducing gene expression or modifying chromatin were well-known in the art, as referenced in the present specification. Therefore, this information need not be specifically disclosed in (and is preferably omitted from) the present specification, since it is information that is well-known to those of ordinary skill in the art. Hence, the that specific disclosure of such methods is not present in the specification does not render it non-enabling for claims 14 and 15.

Applicants also respectfully assert that the Examiner's reliance on *Genentech* is unfounded. The issue in *Genentech* was whether or not the specification enabled claims to unspecified enzymatic cleavage of unspecified amino acid sequences, when the specification contained limited information regarding which enzymes or amino acid sequences might be appropriate and when the prior art taught *away* from the only enzyme-amino acid combination that *was* taught in the specification. The situation in the present case is quite distinct. Here, the means of inducing gene expression or chromatin alterations are not claimed *per se*, but are only recited generically as known methods which are used in certain embodiments of the invention as presently claimed to carry out a genetic modification at a target locus in a nuclear donor cell. In addition, the Examiner has pointed to nothing in the prior art that teaches *away*

from the ability of one of ordinary skill to use a variety of art-known methods, such as those referred to in the specification, to carry out this genetic modification. "Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling." *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Finally, unlike in *Genentech* where the specification was held not to describe the production of a protein by the claimed process "in any detail," *see Genentech,* 108 F.3d at 1365, genetic modification at a target locus in a nuclear donor cell is indeed described and even exemplified in great detail in the present specification. All of this is contrary to the situation in *Genentech*, since in that case the specification was so insufficient that ordinarily skilled artisans were unable to produce human growth hormone by the disclosed process for nearly five years post-filing. *See Genentech*, 108 F.3d at 1367. Hence, *Genentech* is easily distinguished from the situation in the present case, and the Examiner's reliance on that case to support the present rejection is clearly unfounded as the present specification presents far more than just a "germ of an idea" in support of the presently claimed invention.

Therefore, in view of the teachings of the present specification and information that is known in the art (which, under *Hybritech*, *Lindemann Maschinenfabrik*, *Wands*, and *Howarth*, need not be taught in, and preferably is omitted from, the present specification), one of ordinary skill would be able to make and use the methods of claims 14 and 15 with a reasonable expectation of success and without undue experimentation. Hence, the present specification fully enables claims 14 and 15 as currently presented.

In view of the foregoing remarks, the rejection of claims 14 and 15 under 35 U.S.C. § 112, first paragraph for lack of enablement, made in the previous Office Action, should not be maintained.

VII. The Rejection Under 35 U.S.C. § 112, Second Paragraph

In the Office Action at pages 8-9, the Examiner rejected claims 1, 3, 5, 9, 10 and 12 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Applicants respectfully traverse this rejection.

A. The Alleged Omission of Essential Steps

In making this rejection, the Examiner first contended that claims 1-17 were unclear for allegedly omitting essential steps. Specifically, the Examiner contends that reprogramming the cell for nuclear transfer (such as by serum starvation), prior to insertion into a recipient cell, is an essential step to the claimed methods. Applicants respectfully disagree with these contentions.

Applicants respectfully disagree that serum starvation is the only method, or even an essential method, by which this reprogramming may be accomplished. As noted above, while serum starvation is the selected method used for making G_0 donor cells in the Examples in the present application (*see, e.g.*, specification at page 51, lines 2-5), it certainly is not the only means of inducing cells to enter the quiescent (*i.e.*, G_0) phase of the cell cycle. Other methods such as chemical treatments, growth inhibition or manipulation of gene expression are well-known in the art (*see, e.g.*, WO 97/07669; Doc. No. AM1, of record, which was incorporated

by reference into the present application; *see* specification at page 1, lines 21-23). Also, as discussed above, other methods of making nuclear donor cells using cells from different stages of the cell cycle were known from the seven patent applications cited in the present specification at page 1, lines 26-27. Hence, Applicants respectfully assert that reprogramming of donor cells by a particular method is not an essential step of the claimed methods. This portion of the rejection therefore should not be maintained.

B. The Recitation of "Genetic Material"

The Examiner next contends that the recitation of "genetic material" in claim 1 renders this claim indefinite, as this term could encompass mitochondrial genetic material which is not included within the scope of the invention. By the foregoing amendments, claim 1 has been amended to replace "genetic material" with -- nuclear genome --. Hence, this portion of the rejection has been fully accommodated, and should not be maintained.

C. The Alleged Improper Markush Grouping

The Examiner next contends that claim 3 is indefinite for containing an improper Markush grouping in that each of the recited modifications allegedly is not distinct from the other modifications recited in the Markush group. Applicants respectfully disagree with these contentions.

Applicants wish to note that it is well documented that the term "gene targeting" covers inactivation, modification, replacement, etc., as described in the present specification (*see, e.g.*, page 29, line 14, through page 30, line 26). However, to expedite prosecution, Applicants have

amended claim 3 as suggested by the Examiner, to delete certain of the species recited in the Markush group of this claim and place them into new dependent claim 63. Hence. this portion of the rejection as been accommodated.

As to the Examiner's contention that "it is not clear how a gene can be modified to upregulate expression unless by gene applicant includes the regulatory sequences associated with the gene," (Office Action at page 8, 5th paragraph, last sentence), Applicants respectfully disagree. As one of ordinary skill would appreciate, there are a variety of ways of modifying a gene that ultimately could result in upregulation of expression of that gene, including but not limited to insertions, deletions, and modifications of one or more nucleotides in the gene, which have nothing to do with the question of whether or not regulatory sequences are associated with the gene. Upon expression of a gene so modified, for example after insertion of the modified gene into an expression vector or otherwise operably linking the modified gene to a regulatory sequence, it is certainly not inconceivable that a certain proportion of the modifications described above would result in enhanced expression (*i.e.*, upregulation) of the gene. Therefore, it is certainly true that in certain contexts and embodiments of the present invention the term "gene" refers to coding sequences that are operably linked to one or more regulatory sequences. However, Applicants respectfully assert that the present invention also encompasses situations wherein a gene can, indeed, be modified to upregulate expression without the term "gene" necessarily encompassing coding sequences and their associated regulatory sequences in a single genetic construct.

In view of the foregoing remarks, Applicants respectfully assert that claim 3 as currently presented particularly points out and distinctly claims the subject matter regarded by

Applicants as the invention. Therefore, this portion of the rejection under 35 U.S.C. § 112, second paragraph, should not be maintained.

D. The Recitation of "A Locus Abundantly Expressed"

The Examiner next contends that claims 5, 9 and 10 are indefinite for reciting "a locus abundantly expressed," stating that the specification does not adequately define this phrase. Applicants respectfully disagree. As noted above, the specification (at page 7, lines 11*ff*) specifically describes the preferable use of a genetic target which is actively transcribed or is adjacent to a genetic locus which is actively transcribed. The specification also describes how other such other intermediately or "abundantly expressed loci" can be identified on the basis of mRNA expression as described in an undergraduate text book which is well-known to those of ordinary skill in the relevant arts:

> Suitable genes would produce mRNAs which fall into the arbitrarily defined intermediate, or abundant class of mRNAs which are present at 300 or more copies of each molecule per cell (Alberts et al. 1994, Molecular Biology of the Cell, Garland Publishing, New York and London).

Specification at page 7, lines 11-14. Thus, one of ordinary skill would readily understand, from the context of the phrase "abundantly expressed loci" in the present specification, what is meant by this phrase as it is used in claims 5, 9 and 10.

As the Board has held:

> [35 U.S.C. § 112, second paragraph] merely requires that the claims set forth and circumscribe a particular area with a reasonable degree of precision and particularity. The definiteness of the claim language employed must not be analyzed in a vacuum, but always in light of the teachings of the

> prior art and of the particular application disclosure as it would be interpreted by one having ordinary skill in the pertinent art.

Ex parte Moelands, 3 USPQ2d 1474, 1476 (Bd. Pat. App. Int. 1987) (citing *In re Moore*, 439 F.2d 1232 (CCPA 1971). Since the meaning of an "abundantly expressed locus" is used in the present specification and claims in the same way that this phrase is used in the well-known art, one of ordinary skill could easily determine the metes and bounds of "a locus abundantly expressed" in claims 5, 9 and 10 as currently presented. Thus, Applicants respectfully assert that these claims comport with the requirements of 35 U.S.C. § 112, second paragraph, as interpreted under *Moelands* and *Moore*. This portion of the rejection therefore should not be maintained.

E. The Recitation of "A Long Region of Homology"

Finally, the Examiner contends that claim 12 is unclear and indefinite for reciting "a long region of homology." Applicants respectfully disagree with this contention. The meaning of the phrase "a long region of homology" as used in claim 12 is abundantly clear from the description at page 7, lines 25-27 of the specification. One of ordinary skill reading this phrase in the context of the description contained in the specification, then, would readily understood what is meant by the phrase "a long region of homology" in claim 12. Thus, Applicants respectfully assert that claim 12 comports with the requirements of 35 U.S.C. § 112, second paragraph, as interpreted under *Moelands* and *Moore*. This portion of the rejection therefore should not be maintained.

F. Summary

In view of the foregoing remarks, Applicants respectfully assert that claims 1, 3, 5, 9, 10 and 12 as currently presented particularly point out and distinctly claim the subject matter regarded by Applicants as the invention. Hence, the rejection of these claims under 35 U.S.C. § 112, second paragraph that was made in the previous Office Action should not be maintained.

VIII. The Rejection Under 35 U.S.C. § 103(a) Over the '595 Application

In the Office Action at pages 9-10, the Examiner provisionally rejected claims 1-3, 5, 9, 10, 12, 13, 16 and 17 under 35 U.S.C. § 103(a) as being obvious over the '595 application. Applicants respectfully offer the following preliminary remarks concerning this rejection.

In making this rejection, the Examiner contended that:

> Applicant has provided evidence in this file showing that the invention was owned by, or subject to an obligation of assignment to, the same entity as 09/377,595 at the time this invention was made. Accordingly, 09/377,595 is disqualified as prior art through 35 U.S.C. 102(f) or (g) in any rejection under 35 U.S.C. 103(a) in this application. However, this applied art additionally qualifies as prior art under subsection (e) of 35 U.S.C. 102 and accordingly is not disqualified as prior art under 35 U.S.C. 103(a).

Office Action at page 10, second full paragraph. Applicants respectfully disagree with these contentions.

Applicants note that subsequent to the issuance of the Office Action, the relevant statute has been amended such that:

> [s]ubject matter developed by another person, which qualifies as prior art only under subsection (e), (f), and or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention

> were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

35 U.S.C. § 103(c). This amendment to 35 U.S.C. § 103(c) "applies to all utility, design and plant patent applications filed on or after November 29, 1999, including . . . continued prosecution applications filed under 37 C.F.R. 1.53(d) . . . ." MPEP § 706.02(l). Since the filing date of the present application is December 30, 1999, and since a Continued Prosecution Application was filed in the present matter on January 18, 2001, the amendment to 35 U.S.C. § 103(c) applies to the present application. As the Examiner has acknowledged, the presently claimed invention and that disclosed in the '595 application were owned by the same person or subject to an obligation of assignment to the same person at the time that the present invention was made. Moreover, as the Examiner has acknowledged, to the extent that the '595 application is available as prior art against the present claims, it is only available under 35 U.S.C. §§ 102(e), (f) or (g). Hence, contrary to the Examiner's contentions, the '595 application is not available as prior art against the present claims under 35 U.S.C. § 103(a).

In view of the foregoing remarks, Applicants respectfully assert that the rejection under 35 U.S.C. § 103(a) over the '595 application that was made in the previous Office Action should not be maintained.

IX. The Rejection Under 35 U.S.C. § 103(a) Over Schnieke in view of Stacey (I) and (II)

In the Office Action at pages 11-12, the Examiner rejected claims 1-13, 16 and 17 under 35 U.S.C. § 103(a) as being unpatentable over Schnieke *et al.*, *Science* 278:2130-2133 (1997) (Doc. AR11, of record; hereinafter "Schnieke"), in view of Stacey *et al.*, *Molec. Cell.*

Biol. 14:1009-1016 (1994) (Ref. "U" cited on the Form PTO-892 attached to Paper No. 6; hereinafter "Stacey I") and Stacy *et al.*, *Proc. Natl. Acad. Sci. USA* 92:2835-2839 (1995) (Ref. "V" cited on the Form PTO-892 attached to Paper No. 6; hereinafter "Stacey II"). Applicants respectfully offer the following preliminary remarks concerning this rejection.

The invention as presently claimed is drawn to methods of preparing somatic cells for nuclear transfer comprising modifying the genetic material of the somatic cell at an endogenous (*i.e.*, a naturally occurring) locus by a genetic targeting event. As the Examiner has acknowledged, Schnieke does not disclose such methods, particularly methods wherein the genetic material of the somatic cell is engineered at a precise endogenous genetic locus. Hence, Schnieke is deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies of Schnieke are not cured by the disclosures of Stacey I and Stacey II. First, applicants note that both Stacey I and Stacey II disclose genetic modification (specifically, in the α-lactalbumin gene rather than in the β-lactoglobulin gene (which is not present in mouse)) of mouse ES cells. Contrary to the Examiner's contention in the Office Action at page 11, lines 17-18, and as the ordinarily skilled artisan would appreciate, ES cells are *not* somatic cells. As the specification of the present application states:

> [t]raditionally, cells can be defined as either "somatic", or "germ-line". Some cells, e.g. ES cells may not fall easily in either of these two traditional categories because they are derived from embryos *before distinct somatic and germ lineages can be distinguished.* Their functional equivalent, EG (Embryonic germ) cells are more easily defined as "germ-line" cells because they are derived from primordial germ cells. *In the present text, the term "somatic" does not cover ES or EG cells.*

Specification at page 5, lines 3-9. Thus, one of ordinary skill reading Schnieke in view of either Stacey I or Stacey II could have obtained no guidance that would have permitted the production and use of *somatic* cells prepared for nuclear transfer by the presently claimed methods.

Second, there is no specific suggestion or motivation that would lead one of ordinary skill to have combined the disclosures of Stacey I and/or Stacey II in order to produce the presently claimed invention. Absent such suggestion and motivation, the cited references may not be properly combined to render the claimed invention obvious. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Thus, the Examiner has not met the burden required to sustain a *prima facie* case of obviousness.

Finally, even if these references could be properly combined (which they cannot) and disclosed all of the elements of the presently claimed invention (which they do not), the present invention provides at least one secondary indication of nonobviousness over such a theoretical combined disclosure of the cited art -- unexpected results -- which has long been recognized as a classical secondary indication of nonobviousness. *See Graham v. John Deere Co.*, 86 S.Ct. 684, 694 (1966); *Custom Accessories v. Jeffrey-Allan Industries*, 807 F.2d 955, 960 (Fed. Cir. 1986); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Specifically, the present application provides surprising and unexpected results relative to those available in the art at the time of filing of the present application. For example, the present application demonstrates for the first time that, contrary to previous teachings, a primary somatic cell can be modified *in vitro* by gene targeting and can subsequently support successful nuclear transfer to produce a healthy animal. Reasons why this would have been a surprising (*i.e.*, a nonobvious) finding include:

- Targeting in primary cells, as opposed to immortalized cells, was *previously thought to be impractical* because the expected low frequency of homologous recombination meant that it would be necessary to transfect and screen large cell populations.[1] This process requires the cells to maintain a normal cell type during a period of cell culture long enough to allow for identification of targeted cell clones. However, the high frequency of homologous recombination actually achieved minimized the time in culture, allowing the cells to remain viable for sufficient time to allow selection of targeted clones for successful nuclear transfer;
- Frequency of successful targeting in somatic cells was previously thought to be significantly lower than in ES cells;[2] and
- Genetic manipulation may disrupt the necessary mechanism which allows a donor nucleus to develop into a healthy animal. The ultimate production of live animals (as shown in the Examples in the present application) is a stringent test for donor cell normality, and success could not have been said to be obvious or expected.

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[1]*See, e.g.*, Finn *et al.*, *Molec. Cell. Biol. 9*:4009-4017 (1989) (Doc. No. AT17 on the Supplemental Information Disclosure Statement ("IDS") filed herewith) (which shows that the frequency of homologous recombination ("HR") is substantially higher in an immortal cell line than in the diploid normal cell line from which it was derived); Thyagarajan *et al.*, *Nucl. Acids Res. 24*:4084-4091 (1996) (Doc. No. AS19 on the IDS filed herewith) (which compares HR levels in a number of immortalized and primary cell lines, and clearly shows that HR frequency in immortalized cells is around 100 times higher than in normal primary cells).

[2]*See, e.g.*, Hanson *et al.*, *Molec. Cell. Biol. 15*:45-51 (1995) (Doc. No. AR18 on the IDS filed herewith) (which states, at page 45, middle of paragraph 2, that "[e]vidence is accumulating that gene targeting in embryonic stem (ES) cells is significantly more efficient than in other cell types."); and Porter *et al.*, *Transplantation 64*:1227-1235 (1997) (Doc. No. AS18 on the IDS filed herewith) (in which the entire paragraph on gene targeting in somatic cells at page 1229 points to the fact that targeting in somatic cells is problematic and major improvements are required both in the manipulation of somatic cells in culture and in the efficiency of gene targeting itself; Applicants contend that such improvements are provided by the presently claimed invention).

One of ordinary skill therefore would have had no reason to have predicted that somatic cells could be prepared for use in nuclear transfer by modifying the genetic material of the somatic cell at an endogenous locus, particularly since somatic cells engineered in this way had never been produced, let alone used in the production of transgenic or chimeric animals, prior to the work of the present inventors. Thus, it is clear that the present invention provides results that were not expected in view of knowledge available in the art as of the filing date of the present application, which the Federal Circuit has recognized as "[o]ne way for a patent applicant to rebut a *prima facie* case of obviousness . . . ." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Moreover, such results were unexpected compared with the closest prior art cited by the Examiner (*i.e.*, Schnieke, Stacey I and Stacey II), which is the standard for judging unexpected results in an obviousness context. *See In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984); *see also In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Therefore, this classical secondary indicator of nonobviousness -- unexpected results -- falls in favor of the presently claimed invention. Hence, under *Graham*, *Custom Accessories* and *Soni*, the invention as presently claimed would not have been considered to have been obvious.

Thus, there was no expectation that Schnieke could have been modified by the use of genetic targeting, such as that described in Stacey I or Stacey II, to arrive at the methods now claimed with any reasonable expectation of success. In addition, the invention as presently claimed is based upon unexpected results. Therefore, the presently claimed invention would not have been obvious over Schnieke, Stacey I and Stacey II, alone or in combination.

In view of the foregoing remarks, Applicants respectfully assert that the rejection under 35 U.S.C. § 103(a) over Schnieke, Stacey I and Stacey II that was made in the previous Office Action should not be maintained.

X. Other Matters

Applicants note that in the Office Action at page 2, second paragraph, the Examiner has acknowledged Applicants' claim for priority under 35 U.S.C. § 119 based on UK priority applications GB 9905033.8 and GB 9917023.5. Applicants also acknowledge the Examiner's comment that certified copies of these applications have not yet been filed, as required for perfection of the priority claim under 35 U.S.C. § 119(b). Certified copies of these priority documents will be filed in the present case upon their receipt by the undersigned from the UK Patent Office.

XI. Conclusion

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

It is respectfully believed that this application is in condition for immediate examination. Early notice to this effect is respectfully requested. If the Examiner believes, for

any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/475,674	12/30/99	COLMAN A	1966.002000

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EXAMINER	
CROUCH, D	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/475,674	Colman et al
Examiner	**Group Art Unit**
Deborah Crouch	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-17* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

- ☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3 and 4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

The preliminary amendment filed December 30, 1999 has been entered. Thus claims 1-17 are pending.

Acknowledgment is made of applicant's claim for foreign priority based on two application filed in Great Britain on March 4, 1999 (9905033.8) and August 4, 1999 (99 17023.5). It is noted, however, that applicant has not filed a certified copy of either application as required by 35 U.S.C. 119(b).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3,5,9,10,12,13,16 and 17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 24 and 25 of copending Application No. 09/377,595. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims and claims 24 and 25 of '595 are of overlapping and obvious scope. Instant claims 1-3,5,9,10,12,13,16 and 17 are to a method of preparing a somatic cell for nuclear transfer comprising modifying the genetic material of the somatic cell by a genetic targeting event, where the genetic targeting event is mediated by homologous recombination, where the modification is by transgene placement, where the gene

targeting event is carried out at a locus abundantly expressed in the somatic cell, where a structural gene is placed adjacent to an endogenous promoter, where the endogenous promoter is a milk protein gene, where the targeting vector comprising a long region of homology to a target locus, where the targeting vector is in a circular form, wherein the somatic cell is a primary somatic epithelial, fibroblast, or endothelial. Claims 24 and 25 of '595 are drawn to a process for targeting a transgene to a location of interest comprising selecting a transfected nuclear donor cell wherein a gene targeting vector was used to place the target transgene at the target locus, and the nuclear donor cell comprising a transgene introduced into the genome at a target locus. Instant claims 1-3,5,9,10,12,13,16 and 17 are obvious over claims 24 and 25 of '595 as the specification therein defines a targeting vector to insert or place the transgene of interest at a locus of interest by homologous recombination (page 14, lines 16-31 and page 41, example 3), and that the locus may be one that induces a high level of expression (page 14, lines 10-16 and page 20, lines 3-9). The specification of '595 additionally teaches targeting using a circular vector (page 41, example 3), and sufficiently long enough regions of homology for recombination (page 46, example 4), and where the somatic nuclear donor cells is a primary epithelial, fibroblast, or endothelial (page 16, lines 26-28, page 43, lines 7-8 and page 45, lines 13-16). The cell of claim 25 of '595 is obvious over instant claims 1-3,5,9,10,12,13,16 and 17 as it is the defined purpose of claim 24 in '595. Therefore, given claims 24 and 25 of '595, it would have been obvious to ordinary artisan at the time of the instant invention to make a method of preparing a somatic cell for nuclear transfer comprising modifying the genetic material of the somatic cell by a genetic targeting event as claimed in instant claims 1-3,5,9,10,12,13,16 and 17.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13,16 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for preparing a somatic cell for nuclear transfer by targeting by homologous recombination to either a collagen locus or a β-lactoglobulin locus a transgene construct comprising a β-lactoglobulin promoter operably linked to a DNA sequence encoding a protein and reprogramming the cells by serum starvation, the method where the targeting event results in a targeted cell clone: randomly targeted cell clone ration of 1:100 when the collagen locus is the targeted loci, does not reasonably provide enablement for the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification only defines abundantly expressed loci as being the either the collagen gene locus or the β-lactoglobulin locus. There is no general definition of the term or means to determine other loci that are "abundantly expressed". The specification states that the use of an abundantly expressed locus is necessary for the invention and there is no guidance as to a locus other than the collagen locus which would provide the claimed 1:100 targeted cell clone: randomly targeted cell clone ratio. The specification provides no evidence as the targeted cell clone: randomly targeted cell clone ration obtained when the β-lactoglobulin locus is targeted.

Furthermore, the specification provides no guidance as to other means of targeting than by homologous recombination. The only teaching is by preparing a vector for homologous recombination. Without some teaching as to those characteristics that makes a locus abundantly expressed, makes a locus be capable of the 1:100 targeted cell clone: randomly targeted cell clone ratio, or other means of targeting a particular locus, the specification fails to enable the claims for their breadth.

The art at the time of filing clearly recognized that some outside event to the donor cell in a nuclear transfer procedure must occur for successful develop of an NT unit. Both reprogramming and nuclear/nucleoli remodeling are events the art regards as necessary for a cell to be complete totipotential, that is for the cell to become competent to give rise to a live birth. Fulka et al state that the success when embryonic cells were used as nuclei donor was likely due to the embryo cells not being completely differentiated at the time of transfer, and thus amenable to undergo full reprogramming (page 848, col. 1, parag. 1, line 1 to col. 2, line 1). Fulka et al sates that complete genomic reprogramming in transplanted nuclei would be accompanied by a sequence of developmental and biochemical changes in the reconstructed embryo that would exactly parallel those detected in normal embryos after fertilization (page 850, col. 2, parag. 1, lines 7-11). Kono states that a break down of the nuclear envelop is necessary for reprogramming, as reprogramming probably requires the contact of the chromatin with the ooplasm (page 76, col. 2, parag. 2, lines 1-6). Wolf et al states that the coordination between cell cycles of donor and recipient cell is important to avoid DNA damage and to maintain correct ploidy of the embryo (Wolf, page 102, col. 2, lines 2-5). Wolf also states, and in support of Kono, that a donor nucleus is reprogrammed by the recipient cytoplasm, where the donor nucleus is reverted to the same morphological and temporal pattern of the zygote (Wolf, page 102, col. 1,

lines 1-4). It is noted that Fulka et al stated that the cloning of adult mammals is very inefficient and highly unpredictable (page 849, col. 1, lines 9-10 and page 850-851, bridg. sent.). Thus the art at the time of filing, recognized that the cloning of mammals required a process where the donor nuclei, by a mechanism that was not clear, were reprogrammed such that the differentiation status of the donor nuclei returned to totipotent. The art also taught that activation of the embryonic genomic occurs at different cell divisions in mammalian embryos, but that reprogramming has to be complete a the time of activation. In mice, reprogramming had to be complete by the second cell division. In cattle sheep activation occurs at the fourth cleavage, and reprogramming is believed to occur slowly over the first or second cell cycles (Fulka et , page 850, parag. 1, lines 16-25). The specification only discloses serum starvation as a means for reprogramming the donor somatic cell nucleus. Without further guidance as to other means for reprogramming donor cell nuclei, the claims are not enabled for their full breadth.

Therefore for the reasons cited above, the skilled artisan would need to engage in an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

Claims 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of preparing a somatic cell for nuclear transfer comprising modifying the genetic material of the somatic cell by a genetic targeting event, wherein the genetic targeting event includes the artificial induction of gene expression or the induction of chromatin changes in the cell, and wherein the genetic targeting event is facilitated

by an agent which inhibits histone deacetylation or by expression in the cell of a factor which stimulates transcription at the target locus.

These claims are not enabled as applicant has not provided guidance as to the means or how to administer the means to artificially induce gene expression or to cause chromatin changes in the cell, or those agents that inhibit histone deacetylation or which factor to express in a cell to stimulate transcription at the target locus. There is no discussion of any mechanism through which to artificially induce gene expression, to cause chromatin change, those agents that inhibit histone deacetylation or the DNA sequence or factor to express in a cell to stimulate transcription at the target locus. There is no guidance as to the amount or form an agent or a factor to be introduced into the somatic cell. Is the introduction at the time of, before or after vector introduction? The specification needs to provide some rudimentary guidance for the factors, their dosages and the time of delivery such that the skilled artisan could implement the claimed invention. Furthermore, the instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk a/S* 42 USPQ2d 1001, at 1005). Applicant only throws out a germ of an idea with regards to claims 14 and 15. Thus at the time of the instant invention, the skilled artisan would have needed to engage in an undue amount of experimentation to implement the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,3,5,9,10 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: reprogramming the cell for nuclear transfer. The specification clearly states that donor cells must be reprogrammed by serum starvation prior to insertion into a recipient enucleated oocyte. This is an essential step to a method of preparing a somatic cell for nuclear transfer and must be in the claims.

Claim 1 does not point out the invention which is to replace a genomic sequence with another genomic sequence. The term "genetic material" included mitochondria, but this is not part of the invention. a suggested re-write of the claim is: a method of preparing ... comprising modifying the genome of the somatic cell by a genetic targeting event.

Claim 3 contains an improper markush grouping as each of the recited modifications is not distinct species from the other modifications. For example, inactivation of a gene encompasses removal of a gene, modification of a gene, gene replacement and transgene placement. Applicant should consider making dependent claims if necessary to circumvent the overlapping of species. Also, it not clear how a gene can be modified to upregulate expression unless by gene applicant includes the regulatory sequences associated with the gene.

Claims 5,9 and 10 state "a locus abundantly expressed". The phrase is unclear and indefinite as the specification does not provide a definition such that the reader could determine

which loci are "abundantly expressed". Further, the lack of a definition, other that specific loci disclosed, does not permit the reader to determine if "abundantly expressed" is a comparison to the same genes in other animals, the transgene versus the endogenous gene or some other factor. The metes and bounds of the claim are not clear.

Claim 12 states "a long region of homology to the target locus". The phrase is unclear and indefinite as the specification does not provide a definition such that the reader could determine "a long region of homology". The metes and bounds of the claim are not clear.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3,5,9,10,12,13,16 and 17 are provisionally rejected under 35 U.S.C. 103(a) as being obvious over copending Application No. 09/377,595 which has a common inventors and assignee with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e) if patented. This

provisional rejection under 35 U.S.C. 103(a) is based upon a presumption of future patenting of the conflicting application. Instant claims 1-3,5,9,10,12,13,16 and 17 are obvious over '595 as '595 teaches targeting using a circular vector (page 41, example 3), and sufficiently long enough regions of homology for recombination (page 46, example 4), and where the somatic nuclear donor cells is a primary epithelial, fibroblast, or endothelial (page 16, lines 26-28, page 43, lines 7-8 and page 45, lines 13-16). The result of the method of targeting is a method of preparing a somatic cell for nuclear transfer comprising modifying the genetic material of the somatic cell by a genetic targeting event.

This provisional rejection might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by a showing of a date of invention for the instant application prior to the effective U.S. filing date of the copending application under 37 CFR 1.131.

Applicant has provided evidence in this file showing that the invention was owned by, or subject to an obligation of assignment to, the same entity as 09/377,595 at the time this invention was made. Accordingly, 09/377,595 is disqualified as prior art through 35 U.S.C. 102(f) or (g) in any rejection under 35 U.S.C. 103(a) in this application. However, this applied art additionally qualifies as prior art under subsection (e) of 35 U.S.C. 102 and accordingly is not disqualified as prior art under 35 U.S.C. 103(a).

Applicant may overcome the applied art either by a showing under 37 CFR 1.132 that the invention disclosed therein was derived from the invention of this application, and is therefore, not the invention "by another," or by antedating the applied art under 37 CFR 1.131.

Claims 1-13,16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnieke et al (1997) Science 278, 2130-2133 in view of Stacey et al (1994) Molec. Cell. Biol. 14, 1009-1016 and Stacey et al (1995) Proced. Natl. Acad. Sci. 92, 2835-2839.

Schnieke et al teach a method of preparing a somatic cell for nuclear transfer comprising modifying the genetic material by transfecting ovine primary fetal fibroblasts, somatic cells, with a DNA construct comprising a DNA sequence encoding human factor IX operably linked to an ovine β-lactoglobulin promoter, and the subsequent use of the transfected ovine fetal fibroblasts as donors in nuclear transfer procedures (page 2130, col. 3, parag. 2, lines 1-7, and parag. 3, lines 1-5, page 2131, Table 1 and 2). The result of the method of Schnieke et al is the production of sheep transgenic for human factor IX (page 2132, col.2, parag. 2). Schnieke et al offers motivation in stating that somatic cell donors for nuclear transfer has advantages over pronuclear microinjection as fewer animals are needed to produce one transgenic animal, and that no surrogate females are wasted gestating nontransgenic animals (page 2132, col. 3, parag. 1). However, Schnieke et al do not teach the production of somatic cells fro nuclear transfer by modifying the genetic material of the somatic cell by engineering the modification at a precise and predetermined location of the cell's genome. Stacey et al (1995) both teach the modification of a mouse β-lactoglobulin genomic sequence by a genetic targeting event in mouse ES cells, a somatic cell (Stacey et al (1995) page 2835, col. 2, parag. 6 and page 2836, col. 1, parag. 4). First, the β-lactoglobulin gene was replaced by homologous recombination with a disrupted β-lactoglobulin sequence (Stacey et al (1995) page 2835, col 2, parag. 6). Then, the disrupted sequence was replaced, also by homologous recombination, with the human β-lactoglobulin gene operably linked to the mouse β-lactoglobulin gene promoter (Stacey et al (1995) page 2836, col. 1, parag. 4). These procedures inactivate, remove, modify and replace the mouse β-lactoglobulin

gene, while also placing the human β-lactoglobulin transgene. The insertion of the mouse-human β-lactoglobulin locus into the mouse genome caused the upregulation of expression as human β-lactoglobulin mRNA was on average 15-fold higher than mouse β-lactoglobulin mRNA (Stacey et al (1995) page 2837, col. 1, parag. 1, lines 12-14). The β-lactoglobulin locus is described in the specification as being abundantly expressed, and the mouse β-lactoglobulin promoter is an endogenous promoter of a milk gene. As the endogenous β-lactoglobulin promoter directs abundant expression, it would obviously do so in any cell type, such as fibroblast cells and endothelial cells, given the discussion in the specification, given the disclosure in the specification. Lipofection is one art known method of introducing DNA into a cell of interest. As successful recombination occurred, the vector obviously contained a sequence of long homology. Stacey et al (1994) teach plasmids, circular DNA, as being involved in the gene targeting event (Stacey et al (1994) page 1010, figure 1). Given the teachings of Schnieke et al using primary fibroblasts, the use of primary endothelial cells, epithelial cells or muscle cells would have been obvious to the ordinary artisan at the time of filing. Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to prepare a somatic cell for nuclear transfer comprising modifying the genetic material of the somatic cell by the genetic targeting event of homologous recombination to inactivate, remove, modify, upregulate or replace a gene, or place a transgene into the genome of the cell as claimed given the teachings of Schnieke et al in view of Stacey et al (1994) and (1995). The method of the combined art would provide a gene targeted cell clone: randomly targeted cell clone ratio of 1:100.

Claims 14 and 15 are free of the prior art. At the time of filing, the prior art did not teach or suggest methods of preparing a somatic cell for nuclear transfer comprising modifying the genetic material of the somatic cell by a genetic targeting event.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

The fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Dr. D. Crouch
July 17, 2000